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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/719,571	09/25/1996	DAVID J. ANDERSON	A-63899-1	9615

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EXAMINER
GRUN, JAMES LESLIE

ART UNIT	PAPER NUMBER
1641	30

DATE MAILED: 11/28/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/719,571	ANDERSON et al.
Examiner	**Art Unit**
James L. Grun, Ph.D.	1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *17 Sep 2001 and 18 Oct 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 4-8, and 12-16* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-8, and 12-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1641.

The Request for a Continued Prosecution Application under 37 CFR § 1.53(d), filed 17 September 2001, is acknowledged. The amendment filed 16 March 2001 has been entered. Claims 1, 2, 4-8, and 12-16 remain in the case. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's previous indication that the requirement for submission of formal drawings is being held in abeyance pending the indication of allowable subject matter is re-acknowledged.

Claims 4-7 and 15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 4-7, "the percentage" lacks antecedent basis and it is unclear what is encompassed by "all of part of a sequence".

In claim 15, "the percentage" lacks antecedent basis and it is unclear what is encompassed by "all of part of a sequence".

Claims 8 and 16, and claims 13-14 as dependent from claim 16, are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Stemple et al (Cell 71: 973-985, 1992) for reasons of record.

Applicant's arguments filed 16 March 2001 and 18 October 2001 have been fully considered but they are again not deemed to be persuasive for the reasons of record that there remains no factual evidence of a difference between what is disclosed in the reference and what is instantly claimed. The examiner would note that, notwithstanding applicant's assertion to the contrary in the response filed 18 October 2001, the advisory action mailed 03 April 2001 does not indicate that this ground of rejection has been overcome or withdrawn. Applicant's substantial repetition of previous arguments drawn to the initially isolated population of the reference were again not found germane or persuasive with regard to the cloned cells of the reference noted in the rejection. The examiner would note again, with regard to claim 8, the disclosure of the reference that cloned cells were obtained which produced only nonneuronal cells such as glial cells (e.g.: page 977, col. 2; Table 2 (G + O); Fig. 7A (G + O)). Applicant's arguments with regard to the different methods of isolation, i.e. "using antibody binding to RET protein" as instantly claimed rather than the antibody to LNGFR, cloning, and serial subcloning of the reference, are also not dispositive of the issues as the process of making a product does not serve to limit or distinguish the same product made by another method from itself. Further, with regard to claim 16 and claims dependent thereupon, applicant admits that at least some of the cells cloned with the method of Stemple et al are also "Nps" (see e.g. specification page 26).

Claims 1, 2, 4-8, and 12-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lo et al (Perspectives Dev. Neurobiol. 2: 191-201, 1994), Stemple et al (Dev. Biol. 159: 12-23, 1993), Stemple et al (Cell 71: 973-985, 1992), and Martucciello et al for reasons of record. In addition to the teachings of the references set forth in the statement of the rejection of record, one of ordinary skill in the art would have had a reasonable expectation of the surface expression of a known transmembrane receptor protein, such as RET as taught in Martucciello et al or Lo et al (pages 192-194), in cells expresssing mRNA encoding that protein as taught in Lo et al, and would have had an extremely reasonable expectation that antibodies known to bind to the extracellular domain of the known transmembrane protein would function for binding thereto.

Applicant's arguments filed 16 March 2001 and 18 October 2001 have been fully considered but they are not deemed to be persuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Moreover, the Examiner recognizes that references cannot be arbitrarily combined and that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Nomiya*, 184 USPQ 607 (CCPA 1975); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin*, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 USPQ 545 (CCPA 1969). Notwithstanding applicant's arguments to the contrary, the teachings of the other references combined with those of Lo et al in the instant rejection under 35 U.S.C. § 103(a) provide the methodological guidance and reagents for cell isolation and culture and a reasonable expectation of success which applicant asserts are lacking in the disclosure of Lo et al. Indeed, Lo et al teach (e.g. pages 194 and 199-200) expression of the c-*ret* gene in proliferating undifferentiated precursor cells, i.e. all primordia of the autonomic neuroendocrine system, the persistence of the marker in at least some stages of lineage commitment including as a progenitor of neuronal cells, and that "the isolation" of these cells

having this valuable marker "for very early stages in neural crest cell lineage diversification," followed by their transplantation or culture "should provide a test of their degree of lineage commitment." An expectation that **isolation should** provide further guidance on the commitment of such cells indicates that the reference, in contrast to applicant's assertions, had more than a reasonable expectation of success of isolating the cells. Applicant urges that Lo et al did not teach the expression of the RET protein by the encoding mRNA detected by the reference and that further experimentation would be required to confirm protein expression at appropriate levels. This is not found persuasive for the reasons set forth above in the addition to the statement of the rejection of record. It is also noted that an invention may be obvious under 35 U.S.C. § 103 even if a great amount of experimentation is required within the teachings of the prior art so long as that experimentation is within the abilities of one of ordinary skill in the art to carry out, i.e., it is routine. Notwithstanding applicant's arguments to the contrary, absolute predictability is not required for one of ordinary skill in the art to have had a reasonable expectation of success in using the well known reagents and methods of the prior art with a marker known to the prior art to be expressed on cell surfaces of cells implicitly containing the gene expressed as the mRNA encoding the protein.

In response to applicant's arguments that RET expression helps to isolate particular lineages of neural crest stem cells, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art, i.e. that the isolation of the cells should be done, cannot be the basis for patentability when the differences would otherwise

be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Applicant's assertion that the speculative development chart in Fig. 6 of Lo et al would teach away from the actual populations isolated is not found persuasive as the various cell populations are recited, in almost all of the instant claims, in the alternative and the reference of Lo et al clearly teaches RET expression in the cells which should be isolated, i.e. autonomic progenitor cells such as the proliferating undifferentiated neural crest precursor cells or those in which the marker persists during stages of lineage commitment including progenitors of neuronal cells and, possibly, glial cells (see e.g. Fig. 6 and page 194). Again, an invention may be obvious under 35 U.S.C. § 103 even if a great amount of experimentation is required within the teachings of the prior art so long as that experimentation is within the abilities of one of ordinary skill in the art to carry out, i.e., it is routine.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (703) 308-3980. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (703) 305-3399.

The phone numbers for official facsimile transmitted communications to TC 1600, Group 1640, are (703) 872-9306, or (703) 305-3014, or (703) 308-4242. Official After Final communications, only, can be facsimile transmitted to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. The above inquiries, or requests to supply missing elements from Office communications, can also be directed to the TC 1600 Customer Service Office at phone numbers (703) 308-0197 or (703) 308-0198.

James L. Grun, Ph.D.
November 26, 2001

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP 1800/1641